The management of the hyperosmolar hyperglycaemic state in adults with diabetes: a summary of a report from the Joint British Diabetes Societies for Inpatient Care

AR SCOTT[1] ON BEHALF OF THE JOINT BRITISH DIABETES SOCIETIES FOR INPATIENT CARE[2] AND THE JOINT BRITISH DIABETES SOCIETIES HYPEROSMOLAR HYPERGLYCAEMIC STATE GUIDELINES GROUP[3]

Abstract

The Joint British Diabetes Societies for Inpatient Care have recently provided guidance on the management of hyperosmolar hyperglycaemic state (HHS), a medical emergency which differs from diabetic ketoacidosis (DKA) through higher mortality and potential for complication by myocardial infarction, stroke, seizures, cerebral oedema and central pontine myelinolysis (the latter possibly precipitated by rapid changes in osmolality during treatment). DKA presents within hours of onset, whereas HHS develops over many days, and its associated dehydration and metabolic disturbances are more extreme. A different therapeutic approach is required for HHS than for DKA. The key points in these guidelines are:

Monitoring of the response to treatment:

- **Measure or calculate serum osmolality regularly to monitor the response to treatment**
- **Aim to reduce osmolality by 3–8 mOsm/kg/h**

Fluid and insulin administration:

- **Use intravenous 0.9% sodium chloride solution as the principal fluid to restore circulating volume and reverse dehydration**
- **Note that fluid replacement alone will cause a fall in blood glucose; withhold insulin until blood glucose is no longer falling with intravenous fluids alone (unless ketonaemic)**
- **An initial rise in sodium is expected and is not itself an indication for hypotonic fluids**
- **Early use of insulin (before fluids) may be detrimental**

Delivery of care:

- **Involve the diabetes specialist team as soon as possible.**
- **Nurse patients in areas where staff are experienced in the management of HHS**

[1] Consultant Diabetologist, Sheffield Teaching Hospitals NHS Trust, UK
[2] Appendix 1
[3] Appendix 2

Address for correspondence: Dr Adrian Scott
Consultant in Diabetes and Endocrinology, Sheffield Teaching Hospitals NHS Trust, Northern General Hospital, Herries Road, Sheffield, S5 7AU, UK.
Tel: +44 (0)114 271 4990
E-mail: Adrian.Scott@sth.nhs.uk

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Abbreviations and acronyms

AVPU	Alert, Voice, Pain, Unresponsive scale
CPM	central pontine myelinolysis
DKA	diabetic ketoacidosis
EWS	early warning scoring system
FRIII	fixed rate intravenous insulin infusion
GCS	Glasgow coma scale
HHS	hyperosmolar hyperglycaemic state
JBDS–IP	Joint British Diabetes Societies for Inpatient Care
LMWH	low molecular weight heparin
SBP	systolic blood pressure

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Introduction

Guidelines for the management of HHS in adults are lacking, in contrast to DKA, but HHS requires a different therapeutic approach to DKA.[1] HHS typically occurs in the elderly, but is presenting in ever younger adults and teenagers,[2-4] often as the initial presentation of type 2 diabetes.[5] Mortality in HHS (15–20%) is higher than in DKA.[6-11] Also, DKA presents within hours of onset, but HHS develops over many days, with more extreme dehydration and metabolic disturbances. Clinical definitions of HHS tend to be contradictory and arbitrary and it is important to note that hyperglycaemia and hyperosmolality are insufficient to make the diagnosis of HHS.[12] Many people with diabetes have severe but transient elevations of blood glucose, the difference between this and HHS being the duration of hyperglycaemia and the accompanying dehydration. Mortality and morbidity in HHS is only partly related to age and comorbidities. Seizures, cerebral oedema and CPM are uncommon but well-described complications of HHS,[13,14] possibly precipitated by rapid changes in osmolality during treatment.[15]

Adherence to/use of specific hospital guidelines (where avail-

able) is variable among admitting teams and inexperienced staff often initially manage these patients. Diabetes specialist teams are rarely involved early, and sometimes never. Accordingly, the JBDS–IP has produced guidance from a multidisciplinary group with considerable experience in this area, for use by any health care professional who manages HHS in adults.[16] The emphasis throughout (evidence-based where evidence exists) is on ensuring that biochemical evaluation must go hand in hand with clinical evaluation.

We present an abbreviated summary of this guidance, to outline the rationale and key aspects of our recommendations. See the full guideline[16] for a detailed account of the HHS care pathway.

Definition and diagnosis

Defining HHS by osmolality alone is inappropriate without taking into account other clinical features. Our survey of hospital guidelines in the UK suggests the following diagnostic criteria would be reasonable:

- High osmolality, often ≥320 mOsm/kg
- High blood glucose, usually ≥30 mmol/L
- Severely dehydrated and unwell

In HHS there is usually no significant ketosis/ketonaemia (<3 mmol/L), though mild acidosis (pH >7.3, bicarbonate >15 mmol/L) may accompany the pre-renal failure. Some patients have severe hypertonicity and ketosis and acidosis (mixed DKA/HHS), perhaps due to β-cell exhaustion as a result of temporary glucotoxicity. These patients may require a modification of this treatment guideline according to which aspect predominates.

Initial assessment

Hyperglycaemia results in an osmotic diuresis (fluid loss 100–220 mL/kg;10–22 L in a 100 kg subject).[17] Extracellular volume depletion requires correction, depending upon the degree of free water and sodium deficit in any individual case (Table 1).

HHS should not be diagnosed from biochemical parameters alone, but osmolality is useful, as an indicator of severity and for monitoring changes on treatment. A constellation of sunken eyes, longitudinal furrows on the tongue and extremity weakness correlates with raised blood urea.[18,19] Severe hypovolaemia may manifest as tachycardia (>100 bpm) and/or hypotension (SBP <100 mmHg).[5,20,21] A validated triage EWS will usually identify patients as being at high risk, but patients with HHS typically look less dehydrated than they are as hypertonicity leads to preservation of intravascular volume.[22-24] Acute impairment in cognitive function may be associated with dehydration and is common where osmolality is >330 mOsm/kg.[25,26] An assessment of cognition should accompany a full history, physical examination and review of drug therapy (although information on the pre-morbid cognitive state is usually absent). HHS and DKA can have marked effects on short- and long-term cerebral function. This may be due to cerebral oedema in severe cases or to the presence of significant electrolyte disturbances, changes in osmolality, dehydration, infection and sepsis, hypoglycaemia during treatment, and renal failure.

The goals of treatment of HHS are to treat the underlying cause and to gradually and safely:

Table 1 Typical fluid and electrolyte losses in HHS[12]

	Typical rates of loss	For a 60kg patient	For a 100kg patient
Water	100–220 mL/kg	6–13 L	10–22 L
Na^+	5–13 mmol/kg	300–780 mmol	500–1300 mmol
Cl^-	5–15 mmol/kg	300–900 mmol	500–1500 mmol
K^+	4–6 mmol/kg	240–360 mmol	400–600 mmol

- Normalise osmolality
- Replace fluid and electrolyte losses
- Normalise blood glucose

…and to prevent:

- Arterial or venous thrombosis
- Other potential complications e.g. cerebral oedema/CPM
- Foot ulceration

Early senior review by a clinician familiar with the treatment of HHS is essential to confirm the treatment plan and to review progress.

Monitoring

Blood gas analysis for frequent monitoring may be more convenient after an initial laboratory diagnostic sample. Venous rather than arterial samples are sufficient unless oxygen saturation measurement is required. Local facilities will determine the most safe and efficient approach.

Check serum lactate (for type 1 lactic acidosis related to sepsis) and ketones (to exclude significant ketonaemia if 3β-hydroxybutyrate is <1 mmol/L). Blood glucose and ketone measurements require a laboratory-quality controlled device meeting appropriate standards and adherence to procedures.[27]

Rationale for measurement and calculation of osmolality/osmolarity

Intracellular osmotic pressure is exerted principally by potassium, chloride and phosphate ions while extracellular osmotic pressure is primarily dependent upon sodium, chloride and bicarbonate ions. Glucose, lipids and proteins exert osmotic pressure largely in the extracellular space, while urea and ethanol are termed ineffective osmoles, as they move freely move across cell membranes.[23,28] Serum sodium may be reassuringly normal or even low in the presence of hyperglycaemia, due to an osmotic shift of free water into the extracellular fluid and a resultant dilution of serum sodium.

There are many different formulae to calculate osmolality where frequent measurement of osmolality is unavailable; we recommend $2xNa^+$ + glucose + urea, though a more accurate formula has been reported.[29] Urea can be omitted to allow calculation of tonicity (or effective osmolality), especially when someone is hyponatraemic, since hyposmolality indicates risk of cerebral oedema. Urea can be a useful indicator of severe dehydration, however.

Thus:

- A patient with sodium 122 mmol/L, glucose 13 mmol/L, and

urea 23 mmol/L has a calculated osmolality of 280 and an effective osmolality of 257
- A patient with sodium 122 mmol/L, glucose 30 mmol/L, urea 4 mmol/L has a calculated osmolality of 278 and an effective osmolality of 274.

So, the patient with the raised urea has a much lower effective osmolality and is therefore at a greater risk of cerebral oedema should correction of the hyponatraemia be too fast. The hyponatraemia in the patient with a blood glucose of 30 mmol/L is largely dilutional and will correct as the glucose falls (corrected sodium = 122 + (2.4 x 4) = 131.6).[30]

The key parameter is osmolality, largely determined by glucose and sodium. Plot or tabulate these inter-related parameters to follow their rates of change.

High-dependency/level 2 care

Patients with HHS require intensive monitoring. We suggest that the presence of ≥1 of the following may indicate the need for admission to a high-dependency unit /level 2 environment, where the insertion of a central venous catheter to aid assessment of fluid status and immediate senior review by a clinician skilled in the management of HHS should be considered:
- Osmolality >350 mOsm/kg
- Sodium >160 mmol/L
- Venous/arterial pH <7.1
- Hypokalaemia (<3.5 mmol/L) or hyperkalaemia (>6 mmol/L) on admission
- GCS <12 or abnormal AVPU scale
- Oxygen saturation <92% on air (assuming normal baseline respiratory function)
- SBP <90 mmHg
- Pulse >100 or <60 bpm
- Urine output <0.5 mL/kg/h
- Serum creatinine >200 µmol/L
- Hypothermia
- Macrovascular event (e.g. myocardial infarction or stroke)
- Other serious co-morbidity

Treatment

Fluid replacement

The initial goal is expansion of the intravascular and extravascular volume and restored peripheral perfusion. The speed and type of fluid replacement remain controversial,[31-34] although a Cochrane review recommended crystalloid fluids rather than colloid in ill patients.[35] There is no evidence for the use of Ringer's Lactate (Hartmann's solution) in HHS; use 0.9% sodium chloride solution with potassium added as required.[36,37] Existing guidelines encourage vigorous initial fluid replacement. Measure or calculate osmolality hourly initially and adjust the rate of fluid replacement to promote a gradual decline in osmolality.

Fluid replacement will reduce blood glucose. A rapid fall should be avoided (aim for a reduction of 4–6 mmoL/h), especially where insulin is also given, see below.[12] A target blood glucose of 10–15 mmol/L is reasonable.

Reduced osmolality from lower blood glucose will increase serum sodium (a fall in glucose of 5.5 mmol/L will result in a 2.4 mmol/L rise in sodium); a larger increase suggests insufficient fluid replacement, but this is only a concern if the osmolality is not declining concurrently. Thereafter, plasma sodium should fall by ≤10 mmol/L/24 h.[38] Aim to replace approximately 50% of estimated fluid loss within the first 12 h and the remainder in the following 12 h (although the initial severity, renal impairment and co-morbidities may limit the speed of correction). Complete normalisation of electrolytes and osmolality may take up to 72 h.

Ideally, patients will recover quickly enough to replace the water deficit by taking fluids orally. There is no existing evidence base to justify using hypotonic fluids at less than 0.45% sodium chloride. However, if the osmolality is no longer declining despite adequate fluid replacement with 0.9% sodium chloride solution and an adequate rate of fall of plasma glucose is not being achieved, then 0.45% sodium chloride solution should be substituted.

Insulin dose and timing

- If significant ketonaemia is present (3β-hydroxybutyrate >1 mmol/L), this indicates relative hypoinsulinaemia and insulin should be started at time zero.
- Do not start insulin if significant ketonaemia is not present.
- Most patients with HHS are insulin sensitive and rapidly lowering blood glucose may lower osmolality precipitously. Insulin treatment prior to adequate fluid replacement may result in cardiovascular collapse as water moves out of the intravascular space, with a resulting decline in intravascular volume.
- A fixed rate intravenous insulin infusion (0.05 U/kg/h) is recommended, ideally reducing blood glucose by up to 5 mmol/L/h. Reassess fluid intake and renal function once blood glucose has ceased to decline during initial fluid replacement. Insulin may be started at this point or, if already in place, the infusion rate increased by 1 U/h.

Patients with HHS are potassium depleted but less acidotic than those with DKA so potassium shifts are less pronounced, the dose of insulin is lower, and there is often co-existing renal failure. Hyperkalaemia can be present with acute kidney injury and patients on diuretics may be profoundly hypokalaemic. Potassium should be replaced or omitted as required (Table 2).

Anti-infective therapy

As with all acutely ill patients, sepsis may not be accompanied by pyrexia. An infective source should be sought on clinical history

Table 2 Potassium replacement in HHS

Potassium level in first 24h (mmol/L)	Potassium replacement in infusion solution
>5.5	Nil
3.5–5.5	40 mmol/L
<3.5	Senior review as additional potassium required (via central line in High Dependency Unit)

Key messages

- The hyperosmolar hyperglycaemic state is a medical emergency with a high risk of adverse outcome that differs from diabetic ketoacidosis in its clinical characteristics and management
- A key aim is to reduce osmolality by 3–8 mOsm/kg/h through use of intravenous fluids (principally 0.9% NaCl)
- Monitor carefully and do not give insulin unless blood glucose stops falling while giving intravenous fluids (in the absence of ketonaemia)
- Manage patients where staff are experienced in the management of this condition, and seek prompt advice from the diabetes specialist team

and examination and C-reactive protein may be helpful.[39] Give antibiotics when there is clinical, imaging or laboratory evidence of infection.

Anticoagulation

Patients in HHS are at elevated thrombotic risk[40-45] and should receive prophylactic treatment for this (LMWH) throughout admission, unless contraindicated. Consider full anticoagulation for patients with suspected thrombosis or acute coronary syndrome and consider extending prophylaxis beyond the duration of admission in patients deemed to be at high risk.[43]

Hypophosphataemia and hypomagnesaemia are common in HHS. These patients are often elderly and may be malnourished, and the re-feeding syndrome could be precipitated once the person begins to eat. If hypophosphataemia persists beyond the acute phase of treatment of HHS, oral or intravenous replacement should be considered. Magnesium replacement is of unproven benefit and should only be considered if the patient is symptomatic or has symptomatic hypocalcaemia.

Foot protection

These patients are at high risk of pressure ulceration. An initial foot assessment should be undertaken and heel protectors applied in those with neuropathy, peripheral vascular disease or lower limb deformity. Assume a patient is at high risk if too confused or sleepy to cooperate with assessment of sensation. Re-examine the feet daily.[46,47]

Recovery phase

Many patients with HHS are elderly with multiple co-morbidities, and recovery will largely be determined by their previous functional level and the underlying precipitant of HHS. Early mobilisation and good nutrition are essential (give multivitamins and phosphate where necessary, to prevent re-feeding syndrome).

Intravenous insulin can usually be discontinued once the patient is eating and drinking but intravenous fluids may be required for longer if intake is inadequate. Most patients should be transferred to subcutaneous insulin. For patients with previously undiagnosed diabetes or those previously well controlled on oral agents, switching from insulin to other antidiabetic therapy should be considered after weeks-to-months of stability. People with HHS should be referred to the specialist diabetes team as soon as practicably possible after admission. All patients will require diabetes education to reduce the risk of recurrence and prevent long term complications.

Appendix 1: The JBDS–IP Group Belinda Allan; Ketan Dhatariya; Daniel Flanagan; Maggie Hammersley; Rowan Hillson; June James; Johnny McKnight; Rif Malik; Gerry Rayman; Kate Richie; Aled Roberts; Mike Sampson (Chair); Mark Savage; Debbie Stanisstreet; Louise Stuart; Esther Walden; Chris Walton; Peter Winocour (see the full guideline[16] for titles and affiliations).

Appendix 2: Writing Group Geraldine Brennan; Peter Carey; Ketan Dhatariya; Maggie Hammersley; Philippa Hanson; Stuart Ritchie; Mark Savage; Alan Sinclair. Special thanks also to Christine Jones (Diabetes Inpatient Specialist Nurse UK Group administrator). See the full guideline[16] for titles and affiliations.

Conflict of interest None

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